REMARKS

Claims 127-137 will be pending after entry of this Amendment and Response. Claims 1-126 were previously cancelled. Claims 127, 132, 136 and 137 have been amended. Support for the amendments to the claims can be found in the specification, for example, at paragraphs 28, 41 and 69-107; in the original claims; in Figures 8 and 10; and elsewhere in the specification. Therefore, no new matter has been added.

Rejections under 35 U.S.C. § 103(a)

Claims 127-130, 133, 136 and 137 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sullenger *et al.* (U.S. Patent Publication No. 2003/0083294).

Applicants respectfully disagree.

According to *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 U.S.P.Q.2d 1385 (2007) and M.P.E.P. § 2141, the framework for the objective analysis for determining obviousness under 35 U.S.C. § 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Obviousness is a question of law that is based upon underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

1) determining the scope and content of the prior art;

2) ascertaining the differences between the claimed invention and the prior art; and

3) resolving the level of ordinary skill in the pertinent art.

Objective evidence relevant to the issue of obviousness, if present, must also be evaluated. Such evidence, sometimes referred to as "secondary considerations", may include evidence of commercial success, long-felt but unsolved needs, failure of others and unexpected results.

The claimed invention is not obvious in view of the cited reference.

The Claimed Invention

Independent claim 127 has been amended to recite a method comprising the steps: providing a target and a target partner that do not bind to each other in the absence of an aptamer regulator; contacting a mixture of nucleic acids with the target and the target partner under conditions that disfavor efficient binding between the target and the target partner; partitioning nucleic acids bound to a target-target partner complex from unbound nucleic acids; and retaining the nucleic acids bound to the target-target partner complex, thereby identifying an aptamer regulator that binds to a target wherein binding of the aptamer regulator to the target increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer regulator such that binding of the aptamer regulator to the target is a prerequisite for target-target partner complex formation.

Scope and Content of the Cited Art

Sullenger *et al.* ("Sullenger") discloses a method for modulating the activity of an aptamer by administering a regulator that changes (enhances or inhibits) the binding affinity of the aptamer for its target or that degrades or otherwise cleaves, metabolizes or breaks down the aptamer while the aptamer is still exerting its effect. The modulator can be an oligonucleotide, small molecule, peptide, oligosaccharide or aptamer. Thus, Sullenger provides a regulatable therapeutic regime in the course of aptamer therapy.

Differences Between the Claimed Invention and the Cited Art

Independent claim 127, and the claims that depend therefrom, is directed to a method for identifying an aptamer regulator that binds to a target wherein binding of the aptamer regulator to the target increases the binding affinity of the target for a target partner relative to the affinity

of the target for the target partner when the target is not bound by the aptamer regulator. Independent claim 127 also recites that the target and the target partner do not bind to each other in the absence of an aptamer regulator. Therefore, the binding of the aptamer regulator to the target **enables** the binding of the target to the target partner.

On the other hand, Sullenger discloses a method for identifying a modulator that binds to a **pre-existing** complex between an aptamer and a target. As stated in paragraph 22 of Sullenger:

> In an alternative embodiment of the invention, the modulator itself is an aptamer. In this embodiment, a nucleic acid ligand is first generated that binds to the desired therapeutic target. In a second step, a second nucleic acid ligand that binds to the first nucleic acid ligand is generated using the SELEX process described herein or other processes, and modulates the interaction between the therapeutic nucleic acid ligand and the target. In one embodiment, the second nucleic acid ligand deactivates the effect of the first nucleic acid ligand.

The aptamer modulator (second nucleic acid ligand) in Sullenger does not facilitate binding of the first aptamer (first nucleic acid ligand) to the therapeutic target. The first aptamer is able to bind to the target in the absence of the modulator, which is contrary to the claimed invention (step a). The second aptamer in Sullenger binds to a complex between the first aptamer and the target. This is how Sullenger can determine if the second aptamer deactivates the binding of the first aptamer to the target. If the second aptamer functioned as an aptamer regulator, then binding of the second aptamer to the first aptamer would enable binding of the first aptamer to the target.

In addition, Sullenger does not disclose binding under conditions that disfavor efficient binding between the target and the target partner. In fact, each of the steps in Sullenger show binding under conditions that promote binding. If Sullenger used steps that disfavored binding,

then the Sullenger method would not work for its intended purpose because Sullenger would not identify aptamers that bind to targets or modulators that bind to aptamers.

The examiner states on pages 4-5 of the Action that Sullenger does not disclose the phrase "conditions that disfavor efficient binding between the target and the target partner", but that Sullenger's disclosure of contacting conditions such that the modulator binds to the aptamer and enhances the interaction between the aptamer and its target implicitly teaches the conditions of the claimed invention. Applicants agree with the first part of the examiner's statement that Sullenger does not disclose conditions that disfavor efficient binding between the target and the target partner. However, contrary to the examiner's assertion, conditions that disfavor binding between the target and target partner are not implicit in the disclosure of Sullenger. Sullenger discloses a method for identifying a modulator that binds to a pre-existing complex between an aptamer and a target. Sullenger identifies whether modulators enhance or inhibit binding of an aptamer to a target through the use of various binding assays, molecular modeling, or *in vivo* or *in vitro* assays that measure the modification of biological function. Each of these methods determines the effect of the modulator on binding after the modulator is identified. In contrast, in Applicants' invention, the binding of the aptamer regulator to the target is a prerequisite to the binding of the target to the target partner. The method of the invention is a multi-step method that identifies aptamer regulators from the outset, without the need for subsequent testing. It is the method itself, particularly step b), that identifies the aptamer regulator. That is, with Applicants' method, there is no need to identify an aptamer and then test it to determine if it is an aptamer regulator.

The examiner also states on page 5 of the Action that it would have been obvious to use an aptamer as the target in the SELEX method with the specific suggestions per Sullenger to

select for aptamer modulators that enhance the binding of a nucleic acid target to its target partner. For the reasons stated above, Applicants disagree with this statement. In addition, Applicants note that rejections based on obviousness can not be sustained by mere conclusory statements. Rather, there must be some articulated reasoning with some rational underpinnings to support the legal conclusion of obviousness.

Level of Ordinary Skill in the Pertinent Art

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Summary

Applicants submit that after analyzing the cited reference and the claimed invention, as amended, in view of the *Graham* factors, the cited reference does not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 131 and 132 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sullenger *et al.* (U.S. Patent Publication No. 2003/0083294) in view of Griffin *et al.* (U.S. Patent No. 5,756,291).

Applicants respectfully disagree.

The Claimed Invention

Dependent claim 131 recites that the method of the invention further comprises a negative selection prior to the method steps in independent claim 127.

Dependent claim 132 recites the specific steps comprising the negative selection in claim 131.

Scope and Content of the Cited Art

The Sullenger reference was discussed in the previous rejection. In addition, Applicants agree with the examiner's statement on page 6 of the Action that Sullenger does not disclose negative selection.

Griffin *et al.* ("Griffin") discloses methods for identifying oligomer sequences that specifically bind to target molecules. The Griffin methods involve complexation of the target molecule with a mixture of oligonucleotides containing random sequences and sequences that serve as a primer for PCR under conditions wherein a complex is formed with the specifically binding sequences, but not with the other members of the oligonucleotide mixture. The complex is then separated from uncomplexed oligonucleotides and the complexed members of the oligonucleotide mixture are recovered from the separated complex using PCR. The recovered oligonucleotides may be sequenced. Successive rounds of selection using complexation, separation, amplification and recovery can be employed. The Griffin methods may also include a subtraction method for aptamer preparation. The target molecules may be glycoproteins, proteins, carbohydrates, membrane structures, receptors and organelles, such as serum proteins, kinins, eicosanoids and extracellular proteins.

Differences Between the Claimed Invention and the Cited Art

The examiner states that Griffin discloses a negative selection step. However, the negative selection step in Griffin is part of a subtraction method for aptamer preparation. Griffin states that one could use a positive/negative selection approach or a negative/positive selection approach. Griffin further states that the subtraction method is advantageous in enhancing the

specificity of the aptamer obtained to remove members of the starting oligonucleotide mixture that bind to a second substance from which the target molecule is to be distinguished.

The claimed method, on the other hand, employs a negative selection directed to the target partner. That is, the claimed method retains unbound oligonucleotides, which are oligonucleotides that do not bind to the target partner. This way, only aptamer regulators that bind to the target are identified.

The negative selection in Griffin is directed to oligonucleotides that bind to an undesired substance. That is, the Griffin method retains unbound oligonucleotides, which are oligonucleotides that do not bind to the undesired substance. The undesired substance is a substance that is to be distinguished from the target. This negative selection also prevents the oligonucleotide from cross-reacting with the undesired substance.

The examiner states on page 7 of the Action, that when the Griffin method is applied in this case, the undesired substance would be the target or target partner alone and the desired target molecule would be the target and target partner together. Applicants disagree with this statement because it mischaracterizes the claimed invention. As stated previously, an aptamer regulator enables binding between a target and a target partner. An aptamer regulator does not, as recited in step a) of the claims, bind to a pre-existing target-target partner complex.

In addition, the examiner states on page 7 of the Action that the function to be selected is the binding between a target and its target partner facilitated by an aptamer. Applicants also disagree with this statement because it mischaracterizes the claimed invention. Applicants do not select for aptamer regulator function after the method is performed. It is the method itself, particularly step b), that identifies the aptamer regulator. That is, with Applicants' method, there is no need to identify an aptamer and then test it to determine if it is an aptamer regulator.

For the reasons stated above and for the reasons stated in the previous rejection, Applicants disagree with the examiner's statement that it would have been obvious to use an aptamer as the target in the SELEX method with the specific suggestions per Sullenger to select for aptamer modulators that enhance the binding of a nucleic acid target to its target partner.

Furthermore, this rejection only relates to dependent claims. For the reasons stated above and for the reasons stated in the previous rejection, Griffin, when combined with the teachings of Sullenger, does not cure the deficiencies of Sullenger.

Level of Ordinary Skill in the Pertinent Art

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Summary

Applicants submit that after analyzing the cited references and the claimed invention, as amended, in view of the *Graham* factors, the cited references do not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 133-135 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sullenger *et al.* (U.S. Patent Publication No. 2003/0083294) in view of Gold *et al.* (U.S. Patent No. 5,763,173).

Applicants respectfully disagree.

The Claimed Invention

Dependent claim 133 recites that the method of the invention further comprises the step of removing the retained nucleic acids from the target-target partner complex.

Dependent claim 134 recites that the removing is by eluting the nucleic acids with an agonist competitor to the target.

Dependent claim 135 recites that the removing is by contacting the bound nucleic acids with excess free target.

Scope and Content of the Cited Art

The Sullenger reference was discussed in the first rejection. In addition, Applicants agree with the examiner's statement on page 7 of the Action that Sullenger is silent on the exact procedure in the step of dissociating the nucleic acid-target complexes.

Gold *et al.* ("Gold") discloses methods for identifying aptamers to thermostable DNA polymerases. More specifically, Gold discloses aptamers that are capable of binding to the Taq and Tth thermostable DNA polymerases, thereby inhibiting their ability to catalyze the synthesis of DNA at ambient temperatures. This is useful in polymerase chain reaction (PCR) because the presence of the aptamers in the PCR mixture prevents the thermostable DNA polymerase from amplifying background DNA by preventing any DNA synthesis at lowered temperatures prior to or during the cycling reaction.

Differences Between the Claimed Invention and the Cited Art

The examiner states that Gold discloses the specific procedure of eluting bound DNA aptamers with a target competitor, tRNA, to the target polymerase (column 9, lines 15-26).

Applicants disagree.

Column 9, lines 15-26 of Gold recite:

> Once equilibrated at room temperature, the DNA was incubated for 15 minutes with the appropriate target polymerase in the presence of 2 nmoles of tRNA as a competitor. After incubating, hSA was added to the reaction mixture to a final concentration of 0.01%. Polymerase-DNA complexes were separated from unbound DNA by nitrocellulose filtration through a prewet nitrocellulose filter (0.45 μM) under suction. The filter was immediately washed with 20 mL of the binding buffer, 20 mL of 0.5 M urea in the binding buffer, and 0.5 M urea in water. Bound DNA was isolated from the filters by elution and precipitation from ethanol in the presence of carrier tRNA (5 μg).

This passage is taken from Example 1 of Gold. Example 1 describes the experimental procedures used in the selection of aptamers to both the Taq and Tth polymerases. It is clear from the last sentence of this passage that tRNA is not used to elute the bound DNA, but is used to precipitate the DNA. tRNA is commonly used in ethanol precipitation to recover small amounts of DNA by making the pellet visible.

The examiner also states that tRNA is a target competitor of DNA to the DNA polymerase. Applicants disagree. tRNA is not a competitor of DNA in binding to a DNA polymerase because DNA polymerases do not specifically bind to tRNA. tRNA binds to mRNA and to individual amino acids. tRNA is used in the Gold method to block non-specific binding and to reduce background. Even if tRNA is a competitor, it is not an agonist competitor, as is required by the claims.

For the reasons stated above, Applicants disagree with the examiner's statement that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the aptamer modulator SELEX method disclosed by Sullenger by eluting the nucleic acids with an agonist competitor to the target, as taught by Gold, with a reasonable expectation of success because Sullenger specifically refers to the patents of Gold for details of the SELEX method.

Furthermore, this rejection only relates to dependent claims. For the reasons stated above and for the reasons stated in the first rejection, Gold, when combined with the teachings of Sullenger, does not cure the deficiencies of Sullenger.

Level of Ordinary Skill in the Pertinent Art

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Summary

Applicants submit that after analyzing the cited references and the claimed invention, as amended, in view of the *Graham* factors, the cited references do not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Applicants submit that the claims are not obvious in view of the cited references. Accordingly, reconsideration of the rejections and allowance of the claims at an early date are earnestly solicited.

If there are any questions regarding this Amendment and Response or if the undersigned can be of assistance in advancing the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,

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